Vitamin D - Beyond Bones: Its Relationship to Obesity, Metabolic Syndrome, and Diabetes

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Abstract: While vitamin D has long been known as an essential nutrient for the prevention of bone disorders, vitamin D deficiency has recently been linked to a number of chronic disease states. This review analyzes the epidemiological, clinical, and mechanistic data concerning the relationship between vitamin D status and obesity, metabolic syndrome (MetS), and diabetes. The increased understanding of the role of vitamin D has promoted researchers to study vitamin D as a potential target for the prevention and treatment of multiple chronic diseases.

Keywords: Vitamin D, obesity, metabolic syndrome (MetS), diabetes.

INTRODUCTION

Vitamin D historically has been viewed solely as an essential nutrient for the prevention of bone disorders, such as rickets and osteomalacia [1]. However, it is now postulated that low vitamin D status is linked to other common chronic diseases such as hypertension [2], cardiovascular diseases [3], diabetes mellitus [4], and several types of cancer [5]. In a large cohort study, serum calcidiol (25-hydroxyvitamin D, 25(OH)D) concentrations were inversely associated with all-cause and cause-specific mortality. In particular, vitamin D deficiency (25(OH)D concentration <30 nmol/L) was strongly associated with mortality from cardiovascular and respiratory diseases, cancer, and all-cause mortality [6].

Vitamin D's theoretical link to widespread metabolic processes is consistent with the discovery of the mitochondrial enzyme 25-hydroxyvitamin D_3-1α-hydroxylase (1α-hydroxylase) in a broad expanse of cells and tissues [7]. Breast, prostate, lung, skin, lymph nodes, colon, pancreas, adrenal medulla, and brain cells (cerebellum and cerebral cortex) contain the 1α-hydroxylase [7] and can synthesize calcitriol (1,25-dihydroxyvitamin D, 1,25(OH)2D) [8]. In addition, calcitriol, the active form of vitamin D, modulates cell proliferation and differentiation [8].

Furthermore, the obesity epidemic closely parallels that of vitamin D deficiency and recent research suggests that the two conditions may be related [9]. Some studies even propose that deficiency in this vitamin is a potential cause of obesity [10]. As will be described, it is plausible that vitamin D deficiency can have numerous detrimental effects on health including obesity, metabolic syndrome, and type 2 diabetes.

VITAMIN D DEFICIENCY

Many factors contribute to vitamin D deficiency: inadequate exposure to sunlight, lack of vitamin D containing foods in the diet, aging, fat malabsorption syndromes, and increased catabolism of calcitriol and calcidiol [11].

Although the skin can naturally synthesize vitamin D when exposed to the sun's ultraviolet B (UVB) rays, the use of sunscreens can block these rays and decrease the conversion from the precursor into its active form. In fact, a sun protection factor (SPF) of 30 reduces the synthesis of vitamin D in the skin by more than 95% [12]. Nevertheless, the use of sunscreen is increasing in prevalence due to rising concerns surrounding UV exposure and the development of skin cancers. Since melanin acts as an effective sunscreen, those with darker skin exposed to the same amount of ultraviolet radiation will produce less vitamin D than those with lighter skin [13-14]. This supports the finding that there is a higher prevalence of hypovitaminosis D in women of the African American race compared to their white counterparts [14].

Even with a well-balanced diet, it can be difficult to obtain sufficient levels of vitamin D solely via food intake since few foods naturally contain or are fortified with vitamin D. Moreover, food that is fortified is often not adequate enough to counteract vitamin D deficiency [11]. A recent dietary survey indicates that vitamin D intake below recommended levels are common; more than 75% of the population in Germany, the United States, and the United Kingdom do not meet the recommended intakes of vitamin D [15].

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Because the cutaneous synthesis of vitamin D_3 declines with increased age, aging is also a risk factor for vitamin D deficiency if dietary intake or sun exposure does not compensate for decreased synthesis [16]. The Korea National Health and Nutrition Examination Survey (KNHANES IV) linked low vitamin D levels to sarcopenia, the loss of skeletal muscle mass, quality, and strength. This finding supports the correlation between vitamin D deficiency and increased risk of falls in the elderly. Thus, addressing hypovitaminosis D may confer even more benefits than previously understood and prolong the physical capabilities in the elderly through protective effects against osteomuscular-degeneration [17].

Since modification of the gastrointestinal tract influences nutrient absorption, vitamin D deficiency after bariatric surgery is common [18]. With bariatric surgery, and in particular, gastric bypass, nutrients from the diet and general multivitamins do not reliably prevent nutritional deficiencies. Thus, supplementation is often required [19]. However, bariatric patients oftentimes cannot absorb fat-soluble vitamins and can become deficient in vitamin D [20].

Furthermore, vitamin D levels can decrease due to conditions that enhance vitamin D excretion or catabolism. In individuals suffering from nephrotic syndrome, calcidiol binds with vitamin D binding protein and is then lost through the urine [20-21]. Certain medical conditions and drugs can also enhance the catabolism of calcitriol and calcidiol. For instance, medications used to treat HIV/AIDS can contribute to vitamin D catabolism [22-23]. Furthermore, individuals who suffer from disorders, such as primary hyperparathyroidism, chronic granuloma-forming disorders, and some lymphomas, characterized by the increased catabolism of calcifidiol and calcitriol, are at higher risk of hypovitaminosis D [20,24-25].

In summary, there are many prevalent forces that promote vitamin D deficiency. Lack of or blockade of UV rays, dietary insufficiency/malabsorption, or catabolism of vitamin D can all contribute to low levels; the plausible relationship of low levels of vitamin D to chronic disorders will be described in this paper.

VITAMIN D AND OBESITY

A growing body of epidemiological evidence has emerged linking vitamin D with obesity. An inverse relationship has been reported between adiposity and circulating 25(OH)D concentrations, the physiologically relevant marker of vitamin D status [26-30]. Additionally, low circulating concentrations of 25(OH)D were independently associated with increased BMI and fat mass [31-34]. Kamycheva *et al*. reported that the lowest quartile of vitamin D intake (<2.8 μg/day) was an independent predictor of obesity in both men and women [28]. Similarly, Parikh *et al*. concluded that serum 25(OH)D levels were negatively correlated with BMI and body fat mass [33]. In children, low levels of vitamin D have been found to correlate with higher fat levels and BMIs than kids with adequate levels of vitamin D [35]. Rajakumar *et al*. determined that plasma 25(OH)D was inversely associated with BMI, percentage of total body fat, visceral adipose tissue, and subcutaneous adipose tissue [35]. Conversely, higher vitamin D intake and higher serum levels of 25(OH)D have been related to lower adiposity [36]. Caron-Jobin *et al*. analyzed omental and subcutaneous adipose tissue samples from women undergoing gynecological surgeries and determined that serum 25(OH)D was inversely associated with subcutaneous, visceral, and total adipose tissue area, BMI, and total body fat mass [36].

Although a recent review on calcium and/or vitamin D supplementation showed equivocal results as it related to fat loss [37], other authors have provided evidence that supplementation can increase fat oxidation and promote energy loss through increased fecal fat excretion [38]. Further support for the role of vitamin D in body fat reduction was demonstrated from a 12-week, double-blind, randomized, placebo-controlled trial. The vitamin D group had a statistically significant increase in serum levels of 25(OH)D which was correlated with a decrease in body fat mass [39].

There are several theories as to how vitamin D affects weight loss and obesity. The first theory involves calcium's ability to boost metabolic rates [40]. Because vitamin D is essential for the absorption of calcium in the intestines, vitamin D deficiency can result in decreased calcium absorption. Since calcium can increase thermogenesis and thereby boost the body's metabolism, diminishing the amount of intracellular calcium can result in lower metabolic rates. It has been shown in both mice and humans that the higher the levels of calcium there are in a fat cell, the more fat the cell will burn, corresponding to a protective effect against weight gain. Furthermore, there is accumulating evidence from animal and human studies that suggests that dietary calcium may be beneficial for weight management [40]. Alterations in calcium metabolism have been noted in obese patients. For

instance, a 12 week RCT consisting of 53 overweight or obese subjects with very low calcium intake (<600 mg/day) demonstrated that an energy-restricted diet supplemented with calcium and vitamin D_3 resulted in a significantly greater reduction in fat mass compared with those solely on calorie restriction [41]. This reaffirms previous findings that combined supplementation with calcium and vitamin D can aid in body and visceral fat loss [41-43].

Another theory is that obese patients have decreased bioavailability of vitamin D due to sequestration of vitamin D in body fat compartments. Studies with UVB radiation suggest that obesity does not significantly impact the skin's production of vitamin D_3, supporting the bioavailability hypothesis [34].

A third proposed mechanism relates to the effects of vitamin D on appetite and energy consumption. Deficiency in vitamin D can result in the stimulation of the Agouti Related Protein/Neuropeptide Y (AgRP/NPY) and suppression of the pro-Opiomelanocortin/Cocaine-Amphetamin-Regulated Transcription (POMC/CART) pathway. These alterations lead to an increase in appetite and decrease in energy consumption, contributing to obesity [39,44]. Zemel studied 2 groups of transgenic mice on identical caloric diets. Those that expressed the agouti gene responded to low calcium diets with accelerated weight gain and fat accretion, whereas high calcium diets markedly inhibited lipogenesis, accelerated lipolysis, increased thermogenesis and suppressed fat accretion and weight gain [45]. Because the POMC/CART pathway normally functions to suppress feeding and increase energy expenditure when activated, suppression of this pathway can result in overeating and a disruption of energy homeostasis [46].

Another theory linking vitamin D to obesity involves the teleological phenomena. Foss *et al*. proposed that vitamin D originated as a photoreceptor system in primitive organisms and retained this role as UVB radiation-sensitive sensor. Following this theory, a decrease in UV radiation exposure could signal a winter response, which confers endurance to the cold winter environment. The adaptive response would then result in an increase in body size through the accumulation of fat mass (obesity) and winter metabolism (metabolic syndrome) to increase thermogenic capacity. In today's world of abundance, these anomalous adaptations, signaled by the fall of vitamin D levels, could be contributors to the development of common obesity [10].

Vimaleswaran *et al*. suggested that obesity is a causal factor in the development of vitamin D deficiency, rather than vitamin D deficiency being a causal factor in the development of obesity. However, the authors suggest that vitamin D supplementation could provide health benefits regardless of the directionality. If obesity causes vitamin D deficiency, monitoring and treating vitamin D deficiency might potentially reduce some of the adverse health effects of obesity. Conversely, if low vitamin D levels cause obesity, encouraging people to take vitamin D supplements might help with obesity treatment and management [47].

VITAMIN D AND METABOLIC SYNDROME

Metabolic syndrome (MetS) is a disorder of energy storage associated with central obesity, hypertension, hyperglycemia, and dyslipidemia. Serum levels of calcidiol have been known to be inversely correlated with the prevalence of MetS [48-49]. A recent study found that serum calcidiol concentrations ≤23 ng/mL were correlated with up to a 74% increased risk of MetS in comparison to subjects with concentrations of ≥ 34 ng/mL [50]. Furthermore, a cross-sectional survey found similar results. Most notably, the findings were independent of the degree of obesity [51]. Additionally, data from 4,727 black and white young men and women from the Coronary Artery Risk Development in Young Adults study showed that dietary and supplemental vitamin D intake was inversely related to the development of incident MetS over 20 years of follow-up [52]. Using the National Health and Nutrition Examination Surveys (NHANES) 2003-2006, Maki *et al*. evaluated the association of vitamin D intake and vitamin D status with the prevalence of MetS. From this analysis, Maki *et al*. concluded that higher 25(OH)D levels and greater dietary vitamin D intake are associated with reduced prevalence of MetS [53].

Numerous studies have found low serum levels of vitamin D to be correlated with high triglyceride levels [54-56]. Using data from the Third NHANES (7,186 males and 7,902 females 20 years and over), it was determined that the prevalence of high serum triglyceride levels was significantly higher for participants within the first quartile for calcifidiol levels (<21 ng/mL) than in the fourth quartile (≥37 ng/mL) ($P < 0.001$) [54]. Additionally, analysis of the 2001-2004 NHANES data (including 3,577 participants between 12-19 years old) demonstrated that individuals in the lowest quartile for calcifidiol levels (<15 ng/mL) had an increased risk for hypertriglyceridemia than participants

in the highest quartile (>26 ng/mL) [55]. Furthermore, a cross-sectional study of 149 Spanish school children (ages 8 to 13) demonstrated that children with low serum levels of vitamin D (<17.4 ng/mL) had higher triglyceride levels than those with higher levels of vitamin D (≥27.6 ng/mL) [56].

Although epidemiologic and observational studies have suggested that vitamin D deficiency is associated with suboptimal lipid profile, there is still lack of clinical evidence supporting the benefit of vitamin D supplementation on improving lipid profiles [57]. Furthermore, a randomized, placebo-controlled trial demonstrated that the correction of vitamin D deficiency in the short-term does not correct dyslipidemia [58].

Nevertheless, there are several potential mechanisms for the role of vitamin D in lipid metabolism. Lack of vitamin D decreases the ability of the intestines to absorb calcium, which has the ability to lower serum triglyceride levels through the reduction of hepatic triglyceride formation and secretion. Thus, low serum levels of vitamin D can result in low calcium levels and increased serum triglycerides [56,59]. Additionally, vitamin D suppresses serum concentrations of parathyroid hormone (PTH). When vitamin D levels are low, elevated PTH concentrations lead to a reduction in plasma post-heparin lipolytic activity. Consequently, low serum vitamin D levels can result in decreased peripheral removal of triglycerides and contribute to higher triglyceride levels [56,60]. Furthermore, vitamin D can induce the expression of very low density lipoprotein (LDL)-cholesterol receptors on cells like macrophages [61]. As a result, when serum levels of vitamin D are low, the induction of these receptors does not occur and the removal of LDL from circulation is impaired.

Studies of vitamin D and MetS suggest that supplementation may help insulin resistance and impaired glucose tolerance. In a small RCT of 84 women of South Asian origin living in New Zealand, the participants were randomized into either vitamin D supplementation (4000 IU 25(OH)D_3 per day) or placebo for 6 months. Baseline measurements indicated that all of the participants were vitamin D deficient (serum 25(OH)D_3 <50 nmol/L) and insulin resistant [62]. Significant improvements in insulin sensitivity and insulin resistance as well as a decrease in fasting insulin levels were measured in the supplementation group [63]. However, in a meta-analysis including 15 RCTs, George *et al*. concluded that there is insufficient evidence of beneficial effect to recommend vitamin D supplementation in non-deficient patients as a means of improving glucose control or insulin resistance in patients with diabetes or impaired glucose tolerance [64]. More recent research suggests that it may be beneficial to incorporate vitamin D supplementation as part of the treatment of obesity and insulin resistance in adolescences. A RCT with 35 obese adolescences demonstrated that after 6 months, supplementation with vitamin D (4000 IU/day) resulted in a statistically significant decrease in fasting insulin levels and insulin resistance compared with the placebo control group [65].

VITAMIN D AND DIABETES

Because the association of diabetes with latitude and sun exposure, vitamin D deficiency has been examined as a potential culprit in the development of diabetes mellitus [66]. A cross-sectional survey of a New Zealand Polynesian and Caucasian workforce found that individuals recently diagnosed with diabetes mellitus and impaired glucose tolerance had significantly lower serum concentrations of 25(OH)D compared with controls matched for sex, age, and ethnicity [67]. Additionally, analysis of the serum concentrations of 25(OH)D of 6,228 people surveyed as part of NHANES (1988-1994) displayed an inverse association between vitamin D status and diabetes in non-Hispanic whites and Mexican Americans [68]. The 2001-2006 NHANES with 5,806 participants noted that abdominal obesity and insufficient levels of 25(OH)D interact to increase the risk of insulin resistance. Vitamin D insufficiency and obesity are both individual risk factors for insulin resistance. However, when abdominal obesity and insufficient vitamin D levels occur in the same person, the forces promoting insulin resistance are synergistic [69]. In a cohort study, Mattila *et al*. noted a significant inverse association between serum concentrations of 25(OH)D and the risk for type 2 diabetes. Although the study was longitudinal, a major limitation of the study was that blood samples were not collected at the same time of year for all the subjects. Since sun exposure impacts serum vitamin D levels, the discrepancy between the seasons in which blood sample were collected could have impacted the results [70].

When vitamin D supplementation was prescribed to treat vitamin D deficiency, glucose tolerance was found to improve [71]. In a meta-analysis of observational studies, Mitri *et al*. found that vitamin D intake greater than 500 IU/day decreased the risk of type 2 diabetes

by 13% compared with vitamin D intake less than 200 IU/day [4]. Furthermore, the authors reported that individuals with the highest vitamin D status (>25 ng/ml) had a 43% lower risk of developing type 2 diabetes when compared with those in the lowest group (<14 ng/ml). Additionally, with *post hoc* analysis of 2 trials among patients with baseline glucose intolerance, the authors noted that vitamin D supplementation improved insulin resistance [4]. Yet, vitamin D supplementation to decrease insulin resistance and improve glycemic control in vitamin D deficient type 2 diabetic patients have not revealed conclusive results [72].

Several mechanisms for the role of vitamin D and diabetes have been postulated. Vitamin D has been shown to play a regulatory role in the pancreas, especially in the beta cells. Animal models have demonstrated that vitamin D deficiency inhibits pancreatic insulin secretion [66,73]. Moreover, beta cells contain the receptors for calcitriol and the effector portion of the vitamin D pathway, vitamin D-dependent calcium-binding protein (calbindin-D_{28k}) which is known to confer protective effects against cytokine-mediated beta cell death [66,74]. Vitamin D_3 can also prevent interleukin-1 beta (IL-1β) and interferon gamma (IFN-γ) inhibition of insulin synthesis and secretion in beta cells [75].

Studies have suggested that 25(OH)D concentrations are positively associated with adiponectin, a protein hormone involved in glucose regulation. While most of these studies are small, Vaidya *et al*. analyzed data from 2 large populations (1,206 women from the Nurses' Health Study I and 439 men from the Health Professionals Follow-Up Study) and noted an independent association between 25(OH)D and adiponectin using multivariable linear regression [76]. Additionally, lower adiponectin levels correlate with insulin resistance and MetS [77].

Lastly, vitamin D deficiency can result in hyperparathyroidism, which leads to insulin resistance and diabetes through its impact on glucose metabolism [68,78-79]. In fact, parathyroidectomy has been shown to result in the regression of diabetes and impaired glucose tolerance in some patients [80].

VITAMIN D AND INFLAMMATION

Another link between vitamin D and obesity, diabetes, and MetS may be due to its role in inflammation. Research has demonstrated that vitamin D supplementation can reduce inflammation. In a 1-year randomized intervention, overweight and obese subjects took 40,000 IU vitamin D (cholecalciferol) per week, 20,000 IU vitamin D per week, or a placebo. At baseline and after the 1-year intervention, serum levels of pro-inflammatory cytokines, interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high sensitive C-reactive protein (hs-CRP), were measured. Beilfuss *et al*. found significant associations between IL-6, TNF-α, vitamin D and insulin resistance indices at baseline [81]. The authors noted a positive association between levels of TNF-α and insulin resistance, but a negative association between serum 25(OH)D and insulin resistance. After the 1-year intervention with vitamin D, they found a decrease in serum IL-6 levels [81]; IL-6 inhibits adiponectin gene expression which promotes anti-atherogenic and anti-inflammatory activities [77].

Nevertheless, the relationship between vitamin D and certain pro-inflammatory biomarkers is not clear. For instance, in the previously mentioned study, hs-CRP levels were significantly increased, yet neither insulin resistance nor TNF-α were influenced by a 1-year vitamin D supplementation [81]. It is possible that the lack of association between TNF-α and 25(OH)D was due to the fact that the majority of their study population had sufficient levels of vitamin D at baseline and that vitamin D supplementation could have had a more profound effect in vitamin D deficient subjects. Other authors noted a significant negative association between TNF-α and 25(OH)D in 69 healthy women even after accounting for body fat mass, menopausal age, and other confounding factors [82]. Additionally, a number of studies have demonstrated the significant favorable impact of vitamin D supplementation on pro-inflammatory cytokines such as TNF-α, IL-6, and IL-10 in select groups (type 2 diabetic patients [83], infants with congestive heart failure [84], patients on hemodialysis with end stage kidney disease [85], and patients with colorectal neoplasm [86]).

DISCUSSION

There are significant challenges when trying to interpret the vitamin D literature. While vitamin D deficiency has been linked to numerous conditions, the majority of these findings are based on cross-sectional studies and thus, directionality cannot be established (i.e. it remains unclear whether inadequate levels of vitamin D cause the disorder or if the low level of vitamin D is a consequence of the disorder). Secondly, many vitamin D studies have small sample sizes and mixed results, causing meta-analyses to report

"negative" findings. Thirdly, many studies have different doses and duration of supplementation, making direct comparisons difficult.

Because vitamin D deficiency is becoming an increasing problem, clinicians are working to improve early diagnosis and treatment of hypovitaminosis D and help patients take advantage of the health benefits of maintaining adequate serum levels of vitamin D. While vitamin D can be synthesized naturally in the skin of healthy individuals and obtained from supplementation and in the diet through natural and fortified sources, this compound is emerging as a promising therapeutic. Nevertheless, the mechanisms underlying the role of vitamin D in disease states are still not well understood and further research is required to examine the potential of vitamin D supplementation as a possible therapeutic or preventative measure. Furthermore, there is concern that over-supplementation can activate calcium-mediated apoptotic pathway in human adipose tissue [87]. Overall, the parallel between the rise of vitamin D deficiency and the prevalence of obesity, MetS, and diabetes as well as cardiovascular and other diseases have suggested that future researchers target vitamin D as a potential therapeutic for prevention and treatment of chronic diseases [88].

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